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Review

Neuromodulation by Oxytocin and Vasopressin

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Oxytocin (OT) and vasopressin (VP) are two closely related neuropeptides, widely known for their peripheral hormonal effects. Specific receptors have also been found in the brain, where their neuromodulatory actions have meanwhile been described in a large number of regions. Recently, it has become possible to study their endogenous neuropeptide release with the help of OT/VP promoter-driven expression of fluorescent proteins and light-activated ion channels. In this review, I summarize the neuromodulatory effects of OT and VP in different brain regions by grouping these into different behavioral systems, highlighting their concerted, and at times opposite, effects on different aspects of behavior.

Introduction

The neuropeptides oxytocin (OT) and vasopressin (VP) are known to play important roles in the brain. This review examines the acute neuromodulatory effects of OT and VP, considering their activity in the context of a restricted number of behavioral systems. Following a short overview of their molecular properties, production and release, and characteristics of receptor binding and intracellular pathways, this review will focus on their neuromodulatory modes of action. While the neuromodulatory actions of OT and VP are only beginning to be understood, they appear to have a widespread distribution of effects that seems consistent with a diffuse mode of action. Thus, these neuropeptides have been thought to operate by nontargeted release from hypothalamic centers reaching receptors by long-range diffusion. Recently, however, it has become clear that controlled rapid and local release of OT is possible in different brain areas, and similar local delivery can be expected for VP. Thus, it seems possible that their release can be targeted to selected sets of brain regions, possibly occurring in concert or in competition. In this review, I aim to provide a framework that may serve future studies to address the endogenous and targeted modes of actions of these neuropeptides. It considers their neuromodulatory effects across brain regions in the context of distinct behavioral systems: olfaction and social interactions, fear and homeostasis, learning and memory, and sensory and motor systems.

Oxytocin and Vasopressin: Sequence, Synthesis, Release, and Delivery

The Sequences of OT and AVP across Evolution

OT and VP are two closely related neuropeptides, both consisting of nine amino acids that only differ at the 3rd and 8th position (Figure 1). The difference at the 8th position is their most distinguishing feature, where vasopressin possesses in most mammals an arginine and OT a leucine. They have appeared early in evolution with ancestors that can be traced back as far as the snails and annelids. A VP-like peptide, called [Lys^{8}]conopressin, can be found in cones, leeches, and snails (van Kesteren et al., 1995). Segmented worms express the homolog peptide "annetocin" and a number of insects express "inotocin." Invertebrates mostly have only one OT/VP homolog, whereas most vertebrates have two (Caldwell and Young, 2006). It is thought that separate genes for VP and OT have arisen by duplication of a common ancestral gene in jawless fish (cyclostomes) as long as 500 million years ago. In vertebrates, this duplication gives rise to two nona-peptide homologs that share five or more aminoacids with OT/VP (Figure 1). Thus we can find "isotocin & vasotocin" in bony fish; "mesotocin & vasotocin" in lungfish, amphibians, reptiles, and birds; and "OT & phenypressin" in marsupials (Darlison and Richter, 1999). Though most mammals are thought to express OT and arginine-vasopressin (AVP), a new form of OT seems to have arisen in new world monkeys in which the leucine in position 8 has been replaced by a proline (Lee et al., 2011). This change alters protein architecture to a much larger extent than the change from mesotocin to OT, potentially leading to functional changes.

Basic Functions of AVP and OT throughout Evolution

The preservation and even duplication of vasopressin and OT homologs throughout evolution suggest important and basic functions for the organism. Indeed, in the mollusc Lymnaea stagnalis, [Lys^{8}]conopressin, expressed in neuronal and gonadal cells, influences male copulatory behavior (van Kesteren et al., 1995). Similarly, in medicinal leeches, [Arg^{8}]conopressin induces a stereotypical twisting behavior that resembles spontaneous reproductive behavior by acting on a central pattern generator of oscillating neurons in reproductive ganglia M5&6 (Wagenaar et al., 2010). In vocal teleost fish, grunting, an important aspect of reproductive behavior, is affected by arginine vasotocin in males and by isotocin in females (Goodson and Bass, 2000). In some bird species, flock size correlates with mesotocin receptor distribution in the lateral septum; it can be increased by mesotocin administration and decreased by its antagonist (Goodson et al., 2009). In most vertebrate peripheral systems, VP and OT have a role in regulation of body fluids, in certain cases with opposite roles–e.g., VP is important for water retention and OT for milk secretion (Valentino et al., 2010).

VP actions have been suggested to be directed toward protecting homeostasis of the individual (e.g., water retention, blood pressure, circadian rhythms and temperature regulation, increased arousal, and memory), and OT actions directed toward maintenance of the social group and/or species (e.g., ovulation, parturition, lactation, sexual behavior, and social

Peptide sequences of homologs of vasopressin and oxytocin prohormones

Basic structure:

Signal peptide ("SP"=19aa) –"OT/VP" – G–K–R - Neurophysin (=A-A-P-D-L-D-V-R-K-V-S-P + 93 remaining 93 aa)- A- glycopeptide (39 aa)

Individual sequences:

VP (mammals)	SP -	C Y F Q N C P R G (NH2)-----G – K – R - (AAPDLDVRKVSP-+ 93 aa – A- glycopeptide
Lysipressin (Marsupials, Pigs)	SP -	C Y F Q N C P K G (NH2)-----G – K – R - (AAPDLDVRKVSP -+ 93 aa – A- glycopeptide
Phenypressin (Marsupials)	SP -	C F F Q N C P R G (NH2)-----G – K – R - (AAPDLDVRKVSP -+ 93 aa – A- glycopeptide
OT (mammals)	SP -	C Y I Q N C P L G (NH2)-----G – K – R - (AAPDLDVRKVSP -+ 93 aa – A- glycopeptide
OT (New World Monkeys)	SP -	C Y I Q N C P P G (NH2)-----G – K – R - (AALDLDVRKVSP-+ 93 aa – A- glycopeptide
Mesotocin (tetrapods)	SP-	C Y I Q N C P I G (NH2)-----G – K – R - (AAPDLDVRKVSP -+ 93 aa – A- glycopeptide
Vasotocin (Tetrapods/fish)	SP-	C Y I Q N C P R G (NH2)-----G – K – R - (AAPDLDVRKVSP -+ 93 aa – A- glycopeptide
Isotocin (fish)	SP -	C Y I S N C P I G (NH2)-----G – K – R - (AAPDLDVRKVSP -+ 93 aa – A- glycopeptide
Annepressin (annelids)	SP-	C F V R N C P T G (NH2)-----G – K – R - (AAPDLDVRKVSP -+ 93 aa – A- glycopeptide
Conopressin (snails)	SP-	C F I R N C P K/R G (NH2)-----G – K – R - (AAPDLDVRKVSP -+ 93 aa – A- glycopeptide
Inotocin (insects)	SP-	C L I T N C P R G (NH2)-----G – K – R - (AAPDLDVRKVSP -+ 93 aa – A- glycopeptide
Dominant Mutant Pro-VP	SP-	C Y F Q N C L R G (NH2)-----G – K – R - (AAPDLDVRKVSP-+ 93 aa – A- glycopeptide
VP (mammals)	SP -	C Y F Q N C P R G (NH2)-----G – K – R - (AAPDLDVRKVSP -+ Neurophysin II) –A –glycopeptide

Figure 1. Peptide Sequences of Homologous Vasopressin and Oxytocin Prohormones
Top: outline of basic structure for the OT and VP prohormones.
Lower: aligned individual sequences of VP and OT in different species.

interactions) but also suppression of food intake. Therefore, it is tempting to see VP as a "selfish" and OT as an "altruistic" peptide (Legros, 2001). Such an opposite yin/yang action was postulated earlier for central VP and OT function in the rat (Engelmann et al., 2000).

Synthesis and Processing

OT and AVP genes in the mouse, rat, and human genomes are located on the same chromosome separated by a short (3.5–12 kbp) intergenic region but are in opposite transcriptional orientations. In the vertebrate brain, OT and AVP are both synthesized in separate neuronal populations in the hypothalamic paraventricular (PVN) and supraoptic (SON) nuclei as well as in the "accessory nuclei" (AC) that are situated between the PVN and SON (Farina Lipari and Valentino, 1993; Farina Lipari et al., 1995). In addition to AVP, OT neurons are also found in the parvocellular neurons of the PVN and suprachiasmatic nucleus, in the bed nucleus of the stria terminalis (BST), the medial amygdala, the dorsomedial hypothalamus, and the locus coeruleus (Buijs, 1978; Caffé and van Leeuwen, 1983, van Leeuwen and Caffé, 1983), and in rats (but not mice) in the dorsomedial hypothalamus, vertical diagonal band of Broca, and olfactory bulb (Caffé and van Leeuwen, 1983; Tobin et al., 2010). It is possible that this is related with species differences in social behavior.

Expression of AVP and OT in the PVN and SON occurs in strictly separate neuronal populations, principally as a result of differential expression at the mRNA level that seems to be regulated by cis-elements (Gainer, 2012). In contrast to humans, the development of PVN and SON nuclei is late in rodents. Synthesis of AVP in rats starts between day 16 and 18 in utero and that of OT few days after birth (Lipari et al., 2001). Both are stored in secretory granules or vesicles along with their respective carrier proteins, the neurophysins. Neurophysins for the two peptides are of similar molecular weight (10 kDa) with a high percentage of cysteine residues linked by disulfide bridges. Together with AVP/OT, they are synthesized in the cell body as part of a common precursor protein that contains a glycopeptide at the amino end, subsequently AVP/OT, and neurophysin at its carboxy end. Significant processing of this prohormone partly takes place in the granules that contain the enzymes for post-translational processing during their transport to the axon terminal. Thus, for the case of OT, synthesized as nonglycosylated protein, it undergoes endoproteolytic cleavage by the convertase magnolysin to OT-Gly-Lys-Arg (OT-GKR), OT-Gly-Lys (OT-GK), and OT-Gly (OT-G, also known as OT-X) (Brownstein et al., 1980; Burbach et al., 2001). The latter is converted by an alpha-amidating enzyme to the final C-amidated nona-peptide, a step that is vitamin C dependent (Luck and Jungclas, 1987). As a result, release at the nerve endings includes the hormones, the carrier proteins, and residual bits of precursor. Under normal conditions, the release of the final nona-peptide involves a calcium-dependent fusion of the granules with the nerve terminal (Brownstein et al., 1980).

Some mutations (such as P7L AVP) lead to dominant prohormones that are not secreted and accumulate in the endoplasmatic reticulum forming disulfide-linked oligomers that escape degradation, gradually aggregate to fibrillar proteins that cause cell death as in other neurodegenerative diseases (Birk et al., 2009). Prohormones may constitute up to 40% of total OT before birth and have shown increased ratios in 4- to 6-year-old autistic children (Green et al., 2001).

Release and Degradation

Classical neurotransmitters are packaged in small synaptic vesicles that are preferentially localized at synapses. Peptides are stored in large dense-core vesicles (LDCV) which tend to be distributed in soma, in dendrites, and in axonal varicosities as well as at nerve endings. Though both can be released by Ca^{2+}-dependent exocytosis, exocytosis of synaptic vesicles requires a rise of intracellular [Ca^{2+}] in the proximity of presynaptic Ca^{2+} channels, whereas peptide release is triggered

by smaller but broader increases in intracellular [Ca^{2+}]. Such changes in intracellular calcium could be brought about by high-frequency stimulation. Thus, whereas low-frequency stimulation causes a focal increase in Ca^{2+} at the presynaptic membrane and will trigger release of classical neurotransmitters, a more diffuse rise in intracellular Ca^{2+} favors peptide release (Hökfelt, 1991). As a consequence, release of peptide-containing vesicles is considered to be semi-independent from release of small synaptic vesicles (Leng and Ludwig, 2008).

The neuropeptide-containing LDCVs can be released from all parts of a neuron, including the soma and dendrites. Magnocellular neurons of the SON and PVN are densely filled with LDCVs, and their dendrites, representing 85% of the total volume of the neuron, therefore contain very large amounts of OT and AVP. As with presynaptic release, dendritic release is dependent on the increase in intracellular calcium that results from mobilization of intracellular Ca^{2+} stores (Ludwig and Leng, 2006). Intracellular Ca^{2+} stores are extensive in somata and dendrites but often absent from nerve terminals (Sabatier et al., 2007). Some factors can mobilize these stores without any direct increase in spike activity. Among these is α-MSH (α-melanocyte stimulating hormone), originating from preopiomelanocorticoid (POMC)-producing neurons in the arcuate nucleus and acting on melanocortin 4 (MC4) receptors in SON OT neurons (Ludwig and Leng, 2006). The behavioral actions of α-MSH are strikingly similar to those of OT, i.e., inhibition of food intake and stimulation of male sexual behavior, and indeed, it is possible that OT is a mediator of α-MSH actions (Olson et al., 1991).

Peptide-evoked dendritic release is accompanied by another phenomenon of interest for neuronal networks: internal [Ca^{2+}] mobilization can "prime" the secretory vesicles, i.e., make them available for release in response to subsequent electrical stimuli (Ludwig and Leng, 2006) This peptide-induced change in the function of a neuronal compartment produces a reconfiguration of the local neural network, opening new routes for communication between neurons. Priming can last for more than an hour, allowing for long-lasting behavioral effects (Sabatier et al., 2007).

OT and AVP disappear with a half-life of 20 min in cerebrospinal fluid (CSF) (Ludwig and Leng, 2006). What is released centrally is degraded within brain tissue by aminopeptidases or enters the CSF, where it is cleared into the circulation by bulk flow. The aminopeptidases can cleave OT and AVP into shorter peptides, some of which have been shown to facilitate avoidance behavior of rats at concentrations 1000× smaller than AVP, although their efficiency as direct neuromodulators is much smaller than AVP (Burbach et al., 1983, see below).

Diffusion versus Targeted Release

Though axonal fibers containing OT and AVP have been found in a large number of brain areas (see Table 1), local release from dendrites and subsequent diffusion has been proposed to present an important route of action. To estimate the radius of effectiveness of OT released from dendrites, Leng and Ludwig (2008) assumed a basal rate of secretion rate of 0.130 pg/s in a total extracellular hypothalamic space of 10 μl with a half-life of 10 s. Their calculations suggest that a concentration of 260 pg/ml can be achieved in 1 min, which seems consistent with the concentrations of 1000 pg/ml that were measured by microdialysis from the SON (Neumann et al., 1993). This still leaves unclear how OT spreads after release, to where it diffuses, and how quickly and at what concentrations. In the septal nuclei in the forebrain 4–5 mm away from the SON, OT concentrations are raised by stimuli to the SON, but to concentrations 10-fold lower than in the SON itself (Leng and Ludwig, 2008). Though such concentrations may be effective in eliciting responses by OT, it is also clear that delay times for obtaining effects will be considerable. Alternatively, it is possible that OT from the hypothalamus arrives at various brain regions by axonal release from OT containing fibers specifically targeting the brain areas expressing the oxytocin receptor (OTR).

We recently explored this issue by infecting rat PVN, AN, and SON hypothalamic nuclei with a virus construct that assured fluorescent protein and blue light-sensitive Channelrhodopsin-2 expression under the promoter of OT. This revealed an extensive network of OT fibers in various areas of the brain, including the amygdala (Knobloch et al., 2012, see Table 1). It allowed moreover the induction of local OT release from axonal fibers by optical activation using blue light targeted to areas of interest with strong concentration of fibers. In this way, we could show that blue light exposure of the amygdala decreased fear responses to levels similar to those produced by external application of OT targeted to the amygdala through cannulae (Viviani et al., 2011). The effects were blocked by preapplication of OTR

Table 1. Reports for OT and AVP Fibers in Brain Regions in which Their Neuromodulatory Effects Have Been Described

Structure	OT Fibers	VP Fibers
Olfactory bulb	Knobloch et al., 2012	Tobin et al., 2010
Olfactory tubercle	Knobloch et al., 2012	Tobin et al., 2010
Islands of Calleja	Knobloch et al., 2012	
Entorhinal cortex	Knobloch et al., 2012	
MeA	Knobloch et al., 2012	Caffé et al., 1987
BSTma	Knobloch et al., 2012	Caffé et al., 1987
VMH	Griffin and Flanagan-Kato, 2011	Kent et al., 2001
CeA	Knobloch et al., 2012	Caffé et al., 1987
BSTl	Knobloch et al., 2012	Caffé et al., 1987
NTS	Peters et al., 2008	Buijs, 1978; Sofroniew, 1983
DMN	Buijs, 1978; Sofroniew, 1983,	Buijs, 1978; Sofroniew, 1983
N. Ambiguus	Buijs, 1978; Sofroniew, 1983,	Buijs, 1978; Sofroniew, 1983
RVLM	Buijs, 1978; Sofroniew, 1983,	Kc et al., 2010
Parabrachial	van Zwieten et al., 1996.	van Zwieten et al., 1996
Lateral Septum	Sofroniew, 1983	Caffé et al., 1987
Hippocampus	Buijs, 1978; Sofroniew, 1983, Knobloch et al., 2012	Caffé et al., 1987
Spinal cord	Breton et al., 2008; Condés-Lara et al., 2007	Hallbeck and Blomqvist, 1999

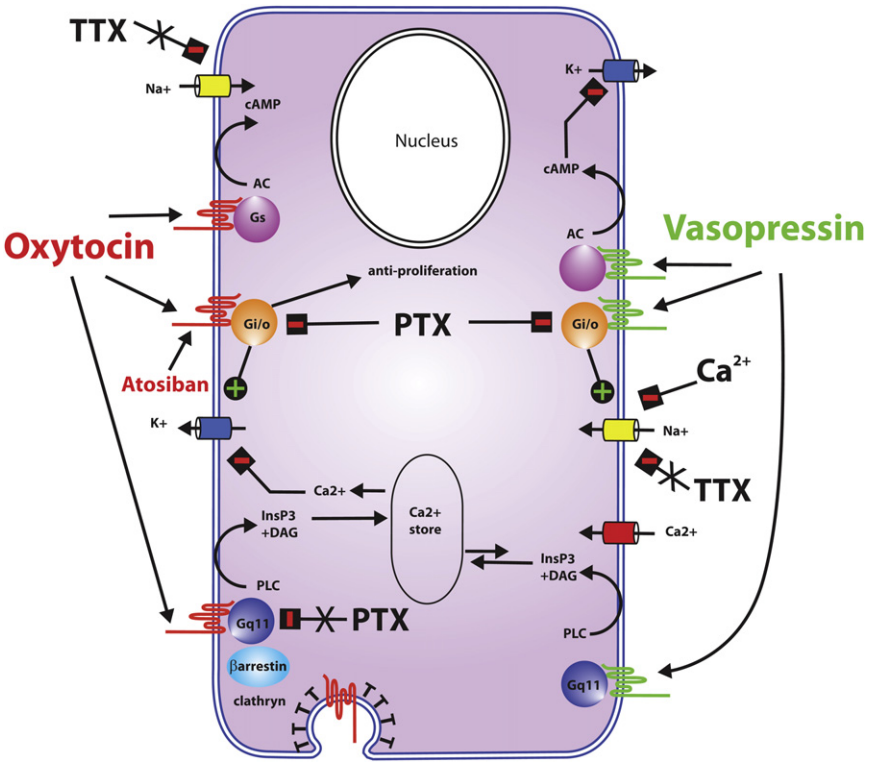

Figure 2. Intracellular Pathways for Oxytocin and Vasopressin

Different intracellular pathways activated by OT or VP according the specific G proteins that they activate, leading to activation of TTX-insensitive Na^+ channels or inhibition of K+ channels. Note the selective recruitment of beta arrestin by Gq11 activation of OT, leading to internalization of the OTR, but not by Atosiban, which only activates the Gi/o-coupled OTR.

antagonists, thereby demonstrating the involvement of OTRs and with it, the effect of endogenous OT release. Decreases in freezing followed as fast as 2 s and on average around 20 s after onset of blue light (Knobloch et al., 2012). Such a short delay time makes it unlikely that these effects of endogenous OT in vivo are due to a diffusion of the nona-peptide from OTergic hypothalamic nuclei.

Taken together, these findings imply an important role of nerve fiber-carried delivery of OT to targets distant from the hypothalamic OT-ergic nuclei. An interesting model has been proposed by Landgraf and Neumann (2004) in which they suggest that axonal release of neuropeptides in limbic area could provide a local precise spatiotemporal, point-to-point regulation of the basal level of neuropeptides, in addition to delivery by continuous diffusion. Neuropeptides could communicate with neurons and modulate different brain structures in a multimodal manner, both through a "wired," axonal, fast, and focal manner as well as in an "unwired," diffusive, slow, and global fashion. Such a "coordinated" dual mechanism of action based on both a diffuse release from neurons in the hypothalamus and their collaterals targeting specific brain structures has recently been proposed by Ross and Young (2009) to underlie the origin of oxytocin in the nucleus accumbens.

Receptors for Oxytocin and Vasopressin

Receptors and Intracellular Signaling

VP receptors (VPRs) and OT receptors (OTRs) belong to the G protein-coupled receptor (GPCR) superfamily, members of which possess seven putative transmembrane domains (TM1-TM7), three extracellular (ECL1-3), and three intracellular (ICL1-3) loops. These receptors seem to have arisen very early in evolution, and, similar to the neuropeptides, it is possible that different receptors for these compounds have appeared through gene duplication and subsequent sequence divergence. Already in the freshwater snail Lymnaea stagnalis, which expresses [Lys^8]conopressin, two receptors can be activated that are expressed in mutually exclusive populations of neurons (van Kesteren et al., 1995). This has been interpreted in support of a theory that OT and VP evolved as ligands for pre-existing receptors. In rodents and human a total of four receptors have been identified based on sequences and ligand binding affinities: OTR, V1a-R, V1b-R, and V2-R. Of these, OTR and V1aR are most abundantly expressed in the brain and will be the focus of further attention.

Agonist binding to GPCRs leads to receptor activation, phosphorylation, and the translocation of beta-arrestin to the receptor complex, an event that disrupts the receptor/G protein interaction and turns off G protein-dependent signaling. The OTR can be coupled to different G proteins leading to different functional effects (Figure 2). OTR coupling to a pertussis-insensitive heterotrimeric Gq/11 protein activates the phospholipase Cβ pathway (PLCβ), which accumulates phosphoinositide and mobilizes intracellular Ca^{2+} mobilization (Wiegand and Gimpl, 2012). This pathway underlies uterus smooth muscle cell contraction (Alberi et al., 1997), increases nitric oxide production, which can lead to cardiomyogenesis (Danalache et al., 2010), and, in neurons, can inhibit inward rectifying conductances (Gravati et al., 2010). In neurons, however, OT can also activate inward rectifying currents through a pertussis-sensitive Gi/o protein, which can moreover signal antiproliferative effects (Gravati et al., 2010). In addition, OT can activate adenylate cyclase via a receptor Gs protein and increase cAMP production, which directly leads, without PKA activation, to a sodium-dependent TTX-resistant sustained inward current (Alberi et al., 1997). It is possible that these various signaling pathways are differentially expressed in neuronal versus peripheral tissues.

Central V1a receptors are also G protein coupled but can signal independently of PLCβ, PKC, or changes in the intracellular Ca^{2+} concentration. Electrophysiological research has shown that AVP and OT can acutely affect neuronal excitability by opening nonspecific cationic channels or by closing K^+

channels. Opening of cationic channels generates a persistent inward current, which can be Na^+ dependent, tetrodotoxin insensitive, and voltage gated, and partially blocked by extracellular Ca^{2+} or Mg^{2+} such as in the case of AVP in facial motoneurons and OT in vagal motoneurons (Raggenbass et al., 1991). In addition, in some motoneurons, AVP can suppress a K^+ current (Ogier et al., 2006) that can be barium sensitive (Kolaj and Renaud, 1998). The intracellular messengers that activate these currents are PKC independent but mediated partially by an AC-cAMP-activated PKA, partially through a yet unknown pathway (Alberi et al., 1997).

Receptor Modulation and Pharmacology

OTRs can reversibly switch between states of 1–100 nM K_d affinity for agonists and antagonists depending on the presence of divalent cations (Mn^{2+}, Mg^{2+}) and specific interactions with membrane cholesterol. Furthermore, cholesterol also appears required for efficient OTR expression and can stabilize the OTR against thermal or proteolytical degradation. Cholesterol-rich microdomains such as caveolae or lipid rafts can thereby switch a growth-inhibitory effect, induced by OT in an MDCK epithelial kidney cell line, into a proliferative response, possibly by recruiting a different signaling cascade (Wiegand and Gimpl, 2012).

In the rat (though not in the mouse, Insel et al., 1993), OTR expression can be increased by estradiol as well as by withdrawal of progesterone at constant estradiol levels. This occurs in a more region-specific manner, possibly as a result of local progesterone and/or estrogen receptor expression, leading to increased binding in the ventromedial hypothalamus (VMH), the principal nucleus of the bed nucleus of stria terminalis (BST), and medial amygdala, but not in the oval BST and central amygdala (Windle et al., 2006 and references therein). Studies on neuromodulation by OT in these areas should therefore be carefully controlled for gender and cycle of the animal.

Upon OT activation, OTRs are phosphorylated by G protein-coupled receptor kinase-2, bind beta-arrestin, and are endocytosed via clathrin-coated vesicles (Smith et al., 2006). After internalization, they recycle back to the plasma membrane via the Rab4/Rab5 short recycling pathway (Conti et al., 2009). This internalization is thought to underlie the rapid desensitization that may occur upon OTR activation. Besides the ability of various G protein isoforms to activate different pathways, Gi selective ligands generate G protein activation without beta-arrestin recruitment and OTR internalization (Busnelli et al., 2012). Interestingly, whereas endogenous OT can activate OTRs regardless to which G protein they are coupled, specific agonists and antagonists may exhibit differential affinity to OTRs, depending on the specific G protein (Gq, Gi, or Go) to which they are coupled and therefore not cause such internalization. Thus, for example, the OTR agonist atosiban does not promote beta-arrestin1 or beta-arrestin2 recruitment and does not affect receptor internalization, possibly because of a selective activation of only those OTR that are coupled to a Gi protein (Busnelli et al., 2012).

It is possible that these differences also underlie the variability in desensitization that has been found across different brain regions. Thus, whereas in the hippocampus, dorsal vagal complex, and VMH, OT can evoke repeatable excitation with very little loss of responsiveness, neurons in the central amygdala (CeA) and lateral division of the dorsal BST (BSTld) exhibit rapid desensitization in spite of high peptide binding (Wilson et al., 2005). This suggests region expression of different receptor types or the occurrence of cell-specific receptor coupling mechanisms and could be of importance in the development of new drugs targeting specific neuropsychiatric diseases (Busnelli et al., 2012).

Though initial agonists and antagonists for VP and OT receptors were mostly peptidergic based, widespread pharmacological efforts have resulted in a number of nonpeptidergic compounds (for excellent review, see Manning et al., 2012). It is important to keep in mind that, though the nomenclature of the receptors suggests otherwise, significant cross-reactivity of these receptors exists for their endogenous ligands OT and AVP. Thus, first of all, AVP binds with a similar affinity to OTRs as it does to the three AVP receptors. The other way round, though OT exhibits more specificity for the OTR, it is still able to bind to VPRs, be it with a 100-fold less affinity (summarized in Mouillac et al., 1995; Manning et al., 2012). This can be particularly important before subscribing specific functions to the endogenous neuropeptides in areas where these different types of receptors are coexpressed.

Receptor Distributions

In the absence of specific and reliable antibodies for VPRs or OTRs, expression levels of both neuropeptide receptors have until now best been addressed by ligand binding studies that rely on labeled specific agonists or antagonists. In the brain, these studies have shown the presence of V1a receptors in the olfactory system, neocortex, basal ganglia, dentate gyrus, BST and CeA, ventromedial hypothalamus, lateral septum, thalamus, circumventricular organs, brainstem, and spinal cord (Raggenbass, 2008). V1b receptors have only been clearly shown in a number of these regions most notably the dorsal one-third of pyramidal cells of the CA2 region, a few cells within the anterior amygdala, and in the PVN (Young et al., 2006). OTRs in the rat brain have most prominently been found in the accessory olfactory bulb, anterior olfactory nucleus islands of Calleja, central and extended amygdala, CA1 of hippocampus, ventral medial hypothalamus, nucleus accumbens, brainstem, and spinal cord.

Interestingly, a number of these studies have shown that in brain regions in which AVP V1a and OTRs are coexpressed, their expression patterns can exhibit remarkable complementarity. This has been beautifully illustrated for the rat extended amygdala and nucleus accumbens by Veinante and Freund-Mercier (1997), who found strong expression levels of OTRs in the lateral part of the CeA, in the shell of nucleus accumbens, and along the further extended amygdala. AVPRs were expressed in the medial part of the CeA (CeM), the core of the nucleus accumbens, and more medially in adjacent areas of the extended amygdala. We have meanwhile shown that functional connections between OTR- and AVPR-expressing regions within the CeA can underlie the opposite effects of AVP and OT on fear behavior (Huber et al., 2005, see below). It may be of interest to examine the presence of such circuitry in other areas exhibiting complementary adjacent expression patterns.

Remarkably few studies have examined the VPR and OTR levels and distributions in humans. These autoradiographic studies typically use the same radiolabeled peptides as used in

rodents although it is not certain that human and rodent receptors exhibit similar binding characteristics. Furthermore, such studies in human brain are typically performed at larger time intervals postmortem as compared to rodent studies though also in the latter it is not clear how much longer intervals affect binding results. Results obtained in brains of humans and other primates for AVP and OT binding have shown some remarkable species differences for OT for example in the basal nucleus of Meynert, subiculum, entorhinal cortex, and amygdala. Binding differences for AVP were less marked though binding was remarkably limited (Loup et al., 1991). A promising field of discovery in this context is the development of reliable radioligands for in vivo PET neuroimaging for OTR or V1aR. Only recently some new promising products have emerged using ^{18}F or ^{125}I and ^{11}C as isotopes, but the use of these compounds is still limited to in vitro studies. The current search is for radioactive ligands that can easily penetrate the blood brain barrier, thereby allowing PET scan studies of OT and AVP receptors levels in living human subjects (Smith et al., 2012).

Differences across Species and Genders and within Lines

Studies on distribution of V1a and OTRs in the brain have shown interesting differences in expression levels between individuals of the same or closely related species and a correlation with striking differences in behavior. The most well-known example of this are the prairie voles in which higher expression levels of OTRs in the female nucleus accumbens and V1aRs in the male lateral septum and ventral pallidum causatively correlate with the formation of stable pair bonds between male and female voles after coupling behavior whereas lower levels lead to less monogamous behaviors (Hammock and Young, 2005; Ross et al., 2009). Except for the lateral septum, surprisingly little electrophysiological research seems to have examined whether OT and AVP exert acute neuromodulatory effects in these regions. The precise mechanism underlying the formation of stable pair bonds remains a field of exploration. It is also possible that these differences in OT/VP signaling create a permissive environment for learning to occur, rather than being directly involved in the induction of the pair bonding (for review see Donaldson and Young, 2008).

A number of rat lines also exhibit a correlation between OT and AVP receptor expression levels and specific types of behavior. Notorious examples are the differences identified by Champagne and Meaney (2001) between high- and low-licking and grooming mother rats characterized by more maternal care and lower anxiety and fear levels. These can be associated with higher levels of OT in the medial preoptic area, paraventricular nucleus, lateral septum, amygdala, and BST, the latter two regions well known for their role in anxiety and fear behavior. A similar association was noticed in mice, bred for different levels of nursing and licking/grooming, between levels of OT and V1a receptors in the lateral septum and frequencies in, respectively, nursing and licking/grooming (Curley et al., 2012). Similarly, LAB/HAB mice and rats show interesting distinctions in AVP and OT signaling that can be related with a large spectrum of different behaviors (Veenema and Neumann, 2007). Such animal models may serve important roles to study similar variations within the human population.

Neuromodulatory Effects of Vasopressin and Oxytocin

The distinct and potentially opposite roles of OT and AVP in the periphery suggest a certain complementary development in the evolution of their functions. In the brain, expression of OT and AVP takes place in nonoverlapping areas, and though at times juxtaposed, remains distinctly separated in different sets of neurons. Similarly their receptors are typically expressed in different regions of the brain, and, where these regions are close neighbors, the expression of their receptors occurs in strictly separate sets of neurons. The question therefore arises of whether it is possible to distinguish across these different brain regions contrasting and complementary roles of the signaling by these neuropeptide receptors. In this section, I will go through the different parts of the brain in which the expression and activation of their receptors have been found and evaluate their functions in light of potential complementary roles.

A large number of electrophysiological studies have already been performed on acute neuromodulatory effects of both peptides in various brain areas. At first glance the effects seem diverse and dispersed in many regions, without a clear organizational pattern. Nevertheless, it may be possible to group some of these regions by considering them as part of neuronal circuits that underlie similar functions. For example, subsets of circuits comprise core networks that integrate the behavioral, physiological, and motivational processes related to specific neural "tasks." Thus, we can identify a core network for social behavior within the limbic system, another network for stress and anxiety, for learning and memory, or more simply sensory and motor tasks (see also Goodson and Kabelik, 2009). Following this approach, in the following parts the hitherto identified neuromodulatory effects of AVP and OT have been tentatively grouped within such networks. Of course, these cannot be strictly segregated, and it should be kept in mind that neurons can participate within several networks; for example, neurons acting with the network underlying social behavior can also contribute to processing within the networks involved in stress and anxiety.

Following an early definition proposed by Kupfermann (1979), neuromodulation, unlike conventional neurotransmission, does not simply excite or inhibit an electrically excitable cell, but is rather involved in altering the effects of other events occurring at the cell. Most reports on the neuromodulatory effects of AVP and OT, however, have up to now only studied effects of external application of these neuropeptides, often resulting in robust changes in spontaneous neuronal activity. However such "spontaneous" activity is typically generated under precise given circumstances in vitro (e.g., changes in external concentrations of Ca^{2+} or K^{+}) that in vivo may depend on conventional neurotransmission. In strictest sense, these studies can therefore not distinguish between a role of OT and VP as conventional neurotransmitters or as neuromodulators. In this context it is important to keep in mind that neuropeptides typically are thought to be coreleased with other classical neurotransmitters such as glutamate or GABA only at higher frequencies of stimulation (Hökfelt, 1991). Consistently, our findings with the blue light-induced stimulation of endogenous release of oxytocin suggest corelease with glutamate (Knobloch et al., 2012) and a similar scenario may apply for vasopressin. The development of optogenetic methods to specifically stimulate OT and AVP

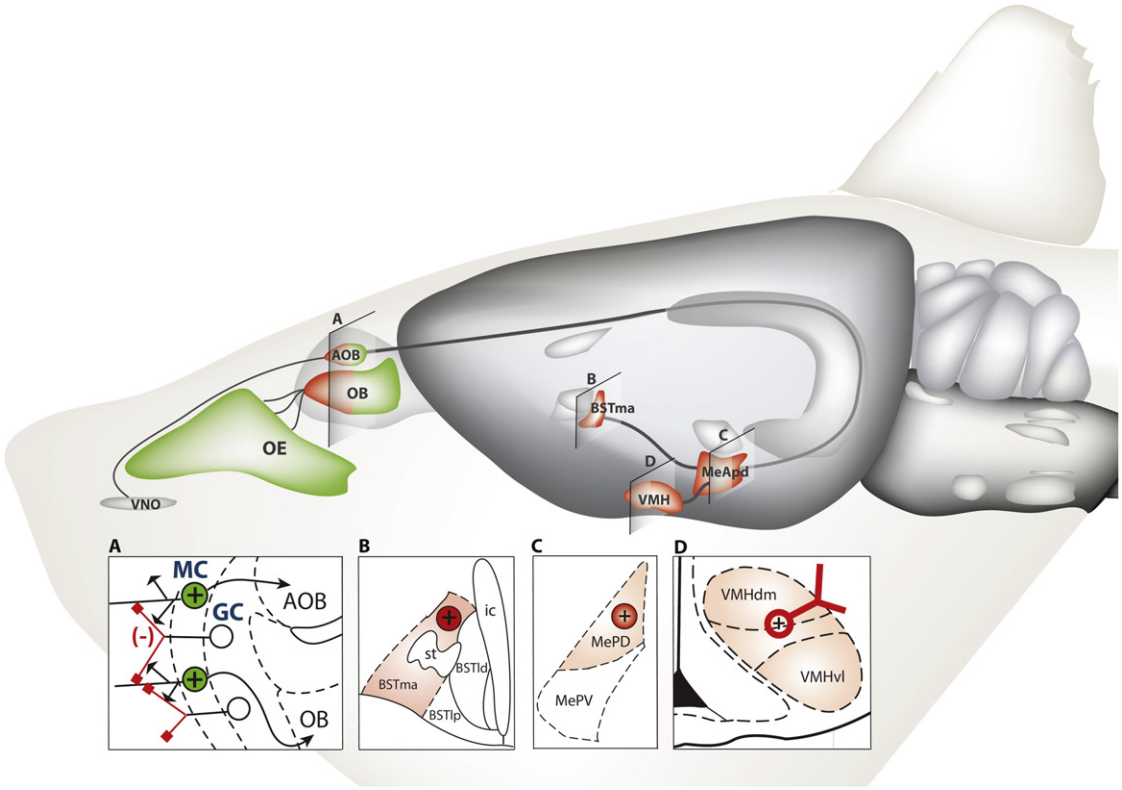

Figure 3. Neuromodulation by OT and AVP of Systems Involved in Social Signaling
OTR-expressing (in red) and AVPR-expressing (in green) regions in the brain and their connections involved in transmitting olfactory stimuli and pheromones to brain regions important for signaling social relevance. Shaded panels indicate levels at which insets were taken that are shown below.
(A) Olfactory bulb showing MCs with cell body excited by AVP and dendrites that excite (arrows) and also in return are inhibited by GC dendrites (squares) that are themselves inhibited by OT.
(B) BSTma-expressing OTRs on cell bodies excited by OT.
(C) Posterodorsal part of medial amygdala (MePD)-expressing OTRs on cell bodies excited by OT (MePV = posteroventral part of medial amygdala).
(D) VMH-expressing OTRs on dendrites that are excited by OT.

containing projections can here provide a most valuable, and possibly even crucial, tool to dissect the precise neuromodulatory roles of these neuropeptides in situ.

Effects in the Olfactory System and on Social Behavior

Olfactory Regions

AVP and/or OTRs are expressed in different regions of the main and accessory olfactory systems. In the main olfactory epithelium, mRNA for both V1a and V1b receptors has been detected (Levasseur et al., 2004). Furthermore, in an immortalized cell line displaying the features of immature, migrating olfactory neurons (GN11), activation of OTRs led to the accumulation of inositol phosphates and to the inhibition of an inwardly rectifying potassium currents (Gravati et al., 2010). No studies seem to have addressed a role in the pheromone-sensitive epithelium of the vomeronasal organ.

At the next level, V1a&bRs as well as OTRs are expressed in both the main (MOB) and accessory olfactory bulb (AOB) (Tobin et al., 2010; Vaccari et al., 1998). Although the MOB and AOB receive distinct inputs from, respectively, the olfactory epithelium and vomeronasal organ, their anatomical organizations appear very similar. In both bulbs, mitral cells (MCs) constitute the main relay neurons. Dendrites of mitral cells make excitatory contact with dendrites of local granule cells (GCs) and in return receive inhibitory dendritic inputs from GCs (Figure 3A). This reciprocal circuit is thought to play a role in the refinement of olfactory and pheromonal signaling. In both mitral and granule cell layers OTR mRNA and OT-immunoreactive fibers have been found (Knobloch et al., 2012; Vaccari et al., 1998; Yoshimura et al., 1993). Neuromodulation by both OT and AVP increased excitability of mitral cells via a V1a receptor (Osako et al., 2000, 2001). Furthermore, the AVP effects could be endogenously triggered by AVP-producing cells that are locally present in the MOB (Tobin et al., 2010). Specific OTR activation caused a decrease of the inhibitory input from GC on MC neurons through a presynaptic mechanism, an effect that seemed important for the induction of maternal behavior (Yu et al., 1996; Osako et al., 2001). It thus appears that in the MOB and AOB, AVP and OT may reinforce each other's actions, AVP by increasing excitation, OT by decreasing inhibition. It has been proposed that, through these concerted actions, both AVP and OT applications to the olfactory bulb also lengthen the retention interval for short-term social odor recognition in male rats (Dluzen et al., 1998). Of interest in this context, OT can lower the threshold for LTP

induction at excitatory synapses between mitral cells and granule cells in the AOB (Fang et al., 2008).

Medial Amygdala and Bed Nucleus of Stria Terminalis

The MOB sends projections to the anterior olfactory nucleus, the piriform cortex, some subdivisions of the cortical amygdala, and the medial amygdala. Most projections to the MeA, however, originate from the AOB (Switzer and DeOlmos, 1985; Swanson and Petrovich, 1998). The AOB also projects to the posterior medial subdivision of the cortical amygdala (COApm) and to the bed nucleus of the stria terminalis (BST) with which the MeA is reciprocally connected (Alheid and Heimer, 1988). This is the major pathway for processing pheromonal cues and important for social interactions (Brennan and Zufall, 2006; Swanson and Petrovich, 1998), and the MeA is for that reason also called the "vomeronasal amygdala." In the MeA of male rats, mRNA for V1aR, V1bR, and OTRs is present and binding of specific OTR antagonists has been demonstrated (Arakawa et al., 2010; Veinante and Freund-Mercier, 1997). Male OT knockout mice lack short-term conspecific social recognition, which can be rescued by local microinjections in MeA of OT prior to the first exposure (Ferguson et al., 2001) and mimicked by antisense oligonucleotides targeting the OTR (Choleris et al., 2007). Interestingly, an OT antagonist injected in the MeA blocked approach behavior to odors of healthy conspecifics, whereas a V1a antagonist blocked avoidance of odor to sick conspecifics, suggesting nonoverlapping, but contrasting, roles for these peptides in this region (Arakawa et al., 2010). In the MeA and the BST, local AVP-producing neurons have been found (Caffé and van Leeuwen, 1983; van Leeuwen and Caffé, 1983) and in the MeA OTergic fibers that originate from the PVN and SON (Knobloch et al., 2012).

Although these findings point to important functions in social behavior for AVP and OT in the MeA and BST, only a few studies seem to have examined neuromodulatory effects in this area. Terenzi and Ingram (2005) showed strong, excitatory effects of OT in the posterodorsal division of the MeA (MePD, Figure 3C), a region with a high density of OT binding sites (Veinante and Freund-Mercier, 1997). These responses were larger and longer lasting, more sensitive and less desensitizing to repeated applications than in the CeA (see below), and no inhibitory responses were found. Ingram's group found similar sensitive nondesensitizing effects of OT in the medial anterior subdivision of the BST (BSTma, Figure 3B, Wilson et al., 2005), a region homologous to the MeA that, interestingly, could be potentiated by oestradiol or progesterone (Wakerley et al., 1998).

Ventromedial Hypothalamus

The OT-sensitive BSTma and MePD are typically activated by sensory stimuli that evoke reproductive behavior. The MePD projects to three interconnected hypothalamic nuclei implicated in reproductive behaviors: the medial preoptic nucleus, the ventral premammillary nucleus, and the ventrolateral part of the ventromedial hypothalamus (VMHvl, Figure 3D, Choi et al., 2005). Activation of these nuclei in females can rapidly induce lordosis (Hennessey et al., 1990). Both OT-containing fibers and OTRs are found in the VMHvl and OT application causes excitation of VMHvl neurons (Kow et al., 1991). Similar to the neuromodulatory OT effects in the BST, these effects were strongly potentiated by treatment with estrogen, though not by progesterone. This is in keeping with the estrogen-induced increases of number of OTRs in the VMHvl, compared to progesterone, which rather seems to cause dendritic extensions and a shifting of OTRs to more distal dendritic locations in the VMHvl (Griffin and Flanagan-Cato, 2011). AVPergic fibers have also been found in the VMH (Kent et al., 2001), but a neuromodulatory has not (yet) been reported.

Taken together, it appears that in circuits involved in processing social olfactory cues, OT and AVP play important neuromodulatory roles by increasing neuronal activity thereby affecting reproductive behavior, including social recognition, induction of lordosis, and maternal behavior. Though on different components of the pathway, both seem to complement and reinforce each other's effects (contrary to a number of strikingly opposite effects they can exert in other systems, see below). In view of the sensitivity to estrogen and progesterone, significant divergence may, however, exist between genders.

Opposite Effects on Alert and Homeostasis

Central Amygdala and BST

OT and AVP show strikingly opposite effects on a number of behavioral aspects of anxiety and fear. Evidence for this was found first in rats, where administration of OT revealed anxiolytic and antistress effects. AVP, on the other hand, increased anxiety-like behavior and visceral responses associated with fear including bradycardia and increases in colonic motility (Bueno et al., 1992, Koolhaas et al., 1998, Roozendaal et al., 1993).

An important area considered to determine these opposite effects was the central amygdala (CeA), a nucleus in the brain that plays an important role as alert center for potentially dangerous stimuli in the environment, and whose activation evokes typical fear responses. Local CeA injections of AVP increased typical fear responses as reflected by a decrease in heart rate and in behavioral motility, and OT increased heart rate and behavioral motility (Roozendaal et al., 1993). The medial part of the CeA (CeM) is the main output of the CeA to the hypothalamus and brainstem areas whose activation underlies the physiological expression of the fear response. It receives projections from the lateral and basolateral amygdala (BLA), where synaptic plasticity has been shown to underlie fear learning (Viviani and Stoop, 2008). The CeA shares many similarities with the lateral part of the BST (BSTl); both structures receive from and project to brain regions that mediate fear-associated behaviors. This similarity in connectivity has led to the notion that the CeA and BSTl are part of a basal forebrain continuum that has been termed the "extended amygdala" (Alheid and Heimer, 1988). Within this structure, it has been proposed that the CeA fulfills an important role in acute (phasic) fear behavior and the BSTl in sustained fear (i.e., anxiety; Walker et al., 2009).

Interestingly, both the CeA and the BSTl show a clear complementary expression of OT and V1aRs (Veinante and Freund-Mercier, 1997) with V1aRs highly expressed in the CeM and OTRs in the adjacent, lateral part of the CeA (CeL). This complementarity can be found throughout the extended amygdala, persisting up to the BSTl (Veinante and Freund-Mercier, 1997; Figure 4). These findings, in combination with the GABAergic projections from the CeL to the CeM subdivision (Jolkkonen and Pitkänen, 1998),

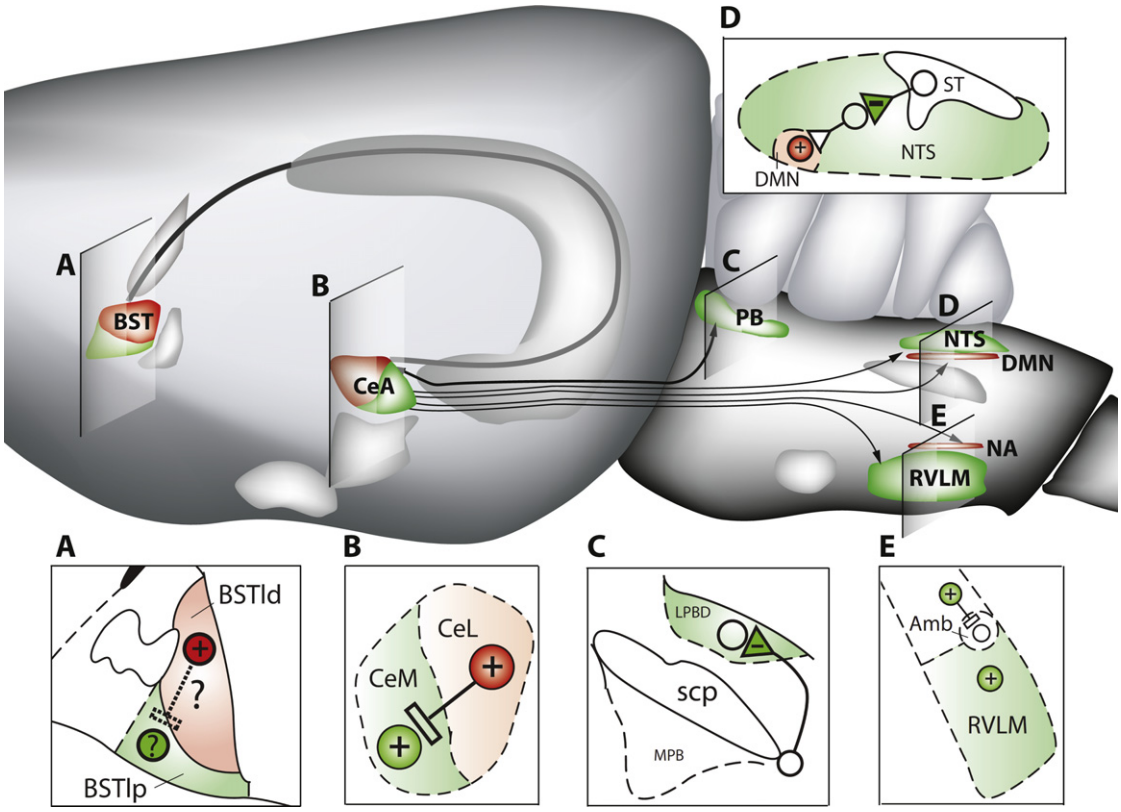

Figure 4. Neuromodulation by OT and AVP in Regions for Alert and Homeostasis

OTR-expressing (in red) and AVPR-expressing (in green) regions in the brain and their connections involved in fear and anxiety. Shaded panels indicate levels at which insets were taken that are shown below.

(A) BST with laterodorsal (BSTld) part expressing OTRs on cell bodies excited by OT and posterolateral (BSTlp) part expressing AVPRs. An inhibitory connection between both areas has been suggested similar to the homologous CeA.

(B) CeA with lateral/capsular part expressing OTRs directly excited by OT and medial part expressing AVPRs directly excited by AVP and indirectly inhibited by OT-activated inhibitory projections from CeL.

(C) Dorsal part of lateral parabrachial nucleus (LPBD) expressing AVPRs with neurons receiving excitatory input from neurons lateral to the superior cerebellar peduncle (scp) that is presynaptically inhibited by AVP (MPB = medial parabrachial nucleus).

(D) DMN neurons directly excited by OT and indirectly inhibited through presynaptic inhibitory effects of AVP on synapses in the NTS.

(E) RVLM neurons directly excited by AVP and NA neurons indirectly inhibited by inhibitory neurons excited by AVP.

suggested a neuronal circuit that could underlie the opposite effects of OT and AVP in the CeA (see below).

The first studies that showed neuromodulatory effects of OT and AVP on cellular activity in the CeA were published by Condés-Lara et al. (1994) and Lu et al. (1997). They laid the basis for a series of investigations in our laboratory concerning the precise role of OT and AVP in the different parts of the CeA (Huber et al., 2005). Starting with extracellular single-unit recordings, we were able to identify two major populations of neurons, one excited by AVP but inhibited by OT, the other only excited by OT and unresponsive to AVP. The effects of AVP were mediated by the V1aR, whereas those of OT were blocked by traditional OTR antagonists and, contrary to OT effects in the MeA (Terenzi and Ingram, 2005), rapidly desensitizing. The inhibitory effects of OT could be reduced by blocking GABAergic transmission, which suggested that they might be indirectly mediated by an increased release of GABA. The excitatory effects, on the other hand, were unaffected by GABA and appeared to be directly mediated, similarly to the findings of Terenzi and Ingram (2005) in the CeA. To investigate the morphology and projections of these excited neurons, we combined sharp electrode recordings with intracellular labeling of individual neurons. Our observations revealed that OT-excited neurons were localized in the CeL, whereas AVP-excited cells were found in the CeM. Subsequent tracing studies showed that the axon collaterals of the OT-excited cells projected far into the CeM, and immunohistochemical staining showed that they were GABAergic. Further whole-cell patch-clamp recordings indeed showed that the inhibitory effects of OT were related with a massive increase of inhibitory GABAergic currents, induced by the activation of the CeL neurons (Huber et al., 2005). The above set of results led us to the development of a model in which the opposing behavioral effects of AVP and OT are caused by a selective activation of two distinct populations: GABAergic neurons in the CeL are activated by OT and project to the CeM, where they exert inhibitory effects on neurons that are directly activated by AVP receptors (Figure 4B). OTergic modulation of the inhibitory projection from the CeL onto the CeM can therefore control

the input to the CeL and the subsequent output from the CeM (Huber et al., 2005). Of potential interest in this context, it deserves mentioning that both the ventral CA1 and subiculum send direct projections to the CeA, especially its capsular part (Cenquizca and Swanson, 2007), which may have the potential to mediate the ventral hippocampal contribution to fear learning (see below).

With the aforementioned homology between the CeA and the BSTl and their high levels of adjacent, nonoverlapping OTR and V1aR binding sites (Veinante and Freund-Mercier, 1997; Figure 4A), the question arises whether opposite effects of OT/AVP can also be found in the BSTl? Though no effects of V1aR activation seem to have been reported yet, strong excitatory effects of OT have been reported (Wilson et al., 2005). Similar to the desensitization differences between the CeA and MeA (Terenzi and Ingram, 2005; see above), OT effects in the BSTl showed faster desensitization compared to the BSTma. Both the CeA and BSTl are reciprocally connected to brainstem centers, particularly the dorsal vagal complex and parabrachial nucleus (Gray and Magnuson, 1987; Moga et al., 1989), and it is possible that OT action in these nuclei is involved in modulating autonomic functions.

Dorsal Vagal Complex, Nucleus Ambiguus, and Rostral Ventrolateral Medulla

The nucleus of the solitary tract (NTS) is the major visceral sensory relay nucleus in the brainstem and receives signals from arterial baroreceptors, chemoreceptors, cardiopulmonary receptors, and other visceral receptors in an ''organ-topic'' manner through inputs from the solitary tract (ST). It is heavily innervated by the CeA and projects back to among others the CeL, as well as to the dorsal motor nucleus of the vagus (DMN) and the rostral ventrolateral medulla (RVLM, Figures 4D and 4E). Through the DMN and RVLM it maintains a reflex arc for the regulation of both cardiovascular (arterial baroreflex) and gastrointestinal responses. The DMN forms with the NTS the so-called dorsal vagal complex (DVC) and is probably the sole source of parasympathetic control of the upper gastrointestinal tract. It mediates the effects of the amygdala on the gastrointestinal system and on the cardiovascular system by decreasing heart rate (Loewy and Spyer, 1990). On the other hand, neurons in the RVLM are the major source of descending input to the sympathetic vasomotor neurons in the spinal cord, which play a major role in increasing tonic and reflex control of blood pressure (Saha et al., 2005).

AVP has been shown to decrease excitatory glutamatergic inputs from the ST to some neurons in the NTS by selectively reducing the probability of release and to others by blocking axonal conduction (Bailey et al., 2006). Contrariwise, OT has been found to excite preganglionic DMN neurons by generating a sustained inward current (Charpak et al., 1984). This was mediated by two pathways, involving a Gq/11 protein that activated PLC and intracellular Ca stores and a Gs-dependent protein that activates cAMP (Alberi et al., 1997). Besides in the DMN, cardiac parasympathetic neurons are also located in the nucleus ambiguus (Amb). Whole-cell recordings of synaptic activity in identified cardiac parasympathetic ambiguus neurons has revealed that AVP can enhance inhibitory input to these neurons by increasing the frequency and amplitude of spontaneous GABAergic inhibitory postsynaptic currents (Wang et al., 2002). Amplitudes of miniature inhibitory synaptic events were not affected, indicating that AVP probably acted at the somatodendritic membrane of presynaptic GABAergic neurons. This effect was suppressed by a selective AVP V1a receptor antagonist and could not be mimicked by an AVP V2 receptor agonist. By decreasing the parasympathetic outflow to the heart, this mechanism could contribute to the AVP-induced stimulation of heart rate and inhibition of reflex bradycardia. Consistent with this, injection of AVP in the RVLM, adjacent to the Amb, increased heart rate and blood pressure, an effect that seemed to be mediated by V1a receptors. The RVLM receives AVPergic projections from the PVN and stimulation of the PVN evoked similar sympathetic responses that could be blocked by V1a receptor antagonists. However, no electrophysiological recordings seem to have been performed yet to show directly such acute neuromodulatory effects of AVP in the RVLM (Kc et al., 2010).

Parabrachial Nucleus

The parabrachial nucleus (PB), located in the pons, reciprocally connects with the CeA and receives input from the NTS. It is considered to be a secondary relay center for nociceptive transmission, gustation, cardiovascular, and respiratory regulation (van Zwieten et al., 1996). Similar to the NTS, it receives sensory and visceral information, among which glutamatergic inputs from baroreceptor afferents (Saleh et al., 1997). It contains two neuronal systems that oppositely affect cardiovascular function, one eliciting pressor-tachycardic responses, the other leading to depressor-bradycardic responses (Chamberlin and Saper, 1992).

Both AVP and OT immunoreactive fibers are present in the rat lateral PB, but AVP fibers predominantly (van Zwieten et al., 1996). This same group found that AVP, via V1a receptors, decreased to 70% excitatory postsynaptic currents (EPSC) evoked by stimulation of glutamatergic inputs from the superior cerebellar peduncle. AVP did not affect postsynaptic responses to direct glutamate application, suggesting a presynaptic site of action (Figure 4C). Interestingly, aminopeptidase inhibition caused a reduction in the EPSC that could be blocked by a V1 receptor antagonist, suggesting an effect (and a degradation) of endogenous AVP.

Similar to the NTS, by reducing excitatory neurotransmission of parasympathetic output, AVP may thus increase heart rate and blood pressure. At the same time, the lateral PB also sends dense projections to the CeL, which are specifically involved in processing and relaying aversive sensory information and are necessary for taste aversion learning (Fanselow and Dong, 2010) and AVP may also affect this pathway. Though OT-immunoreactive fibers have also been identified in the PB, neither OTRs (Tribollet et al., 1989) nor OTR mRNA have been localized (Chen and Pittman, 1999), and there seem to be no reports on neuromodulatory effects by OT in the PB.

Opposite Effects of OT and AVP on Alert and Homeostasis

Taking the above elements together in the context of alert and homeostasis, an interesting concert of opposite effects for OT and AVP seems to emerge: AVP increases alert for external stimuli by activating the CeM and, at the same time, increases

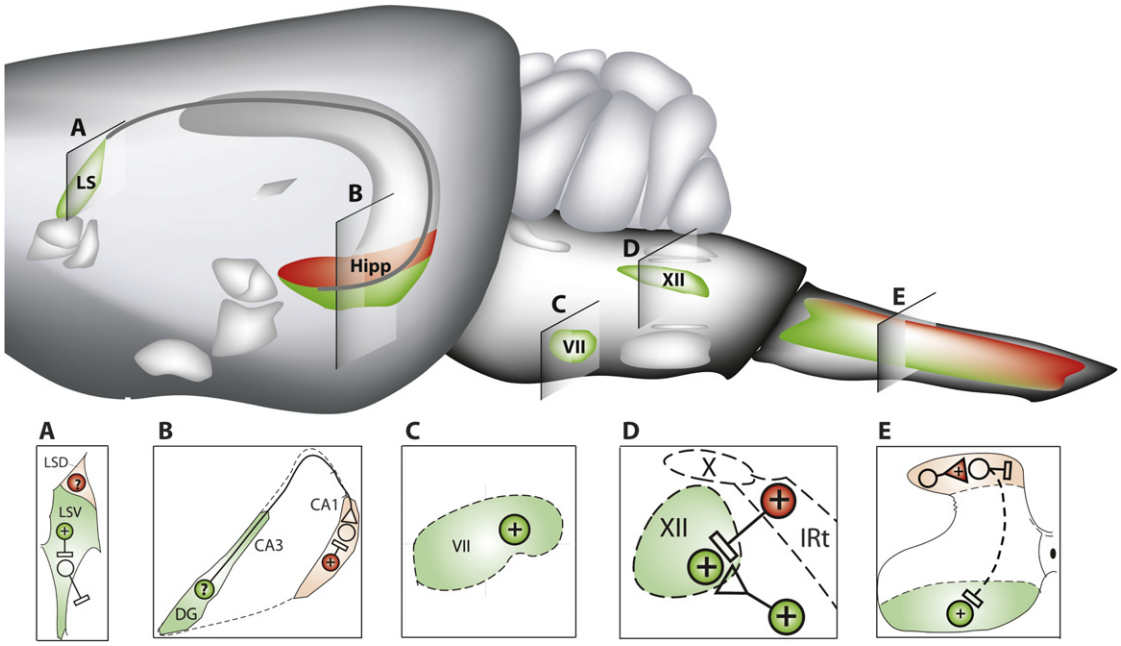

Figure 5. Neuromodulation by OT and AVP of Systems Involved in Memory and Learning, as well as of Sensory and Motor Systems
OTR-expressing (in red) and AVPR-expressing (in green) regions in the brain and their connections involved in memory and learning (left side) and sensory and motor systems (right side). Shaded panels indicate levels at which insets were taken that are shown below.
(A) Lateral septal region (LS) with dorsal part (LSD) expressing OTRs on cell bodies excited by OT and ventral part (LSV) expressing AVPRs on inhibitory neurons inhibiting projections neurons.
(B) Hippocampal region (Hipp) with dentate gyrus (DG)- and CA3-expressing AVPRs and CA1- and subiculum-expressing OTRs on inhibitory interneurons in the pyramidal layer that inhibit pyramidal neurons.
(C) Facial nucleus (VII)-expressing AVPRs on neurons excited by AVP.
(D) Hypoglossal nucleus (XII)-expressing AVPRs on neurons that are directly excited by AVP, indirectly excited by AVP activation of excitatory glutamatergic premotor neurons, and indirectly inhibited by OT activation of inhibitory interneurons releasing GABA or glycine (Wrobel et al., 2010).
(E) Spinal cord expressing OTRs on dorsal side that presynaptically excite local inhibitory neurons and on ventral side AVP-excited neurons which are inhibited by projections from OT-excited neurons, suggested to originate from the dorsal part.

sympathetic output through its excitation of the RVLM and decreases parasympathetic output by inhibiting input to the DVC and output from the Amb and PB. In contrast, OT decreases alert by inhibiting output from the CeM and increases parasympathetic flow by exciting output from the DMN. Together, it is possible that the concerted actions of OT and AVP play an important role for controlling homeostasis when an animal is alerted to external challenges.

Opposite Effects on Memory and Learning

Hippocampus and Subiculum

Receptors for OT and AVP show a clear segregated expression in the ventral hippocampal region (Figure 5). OTRs are found in the CA1 region and the subiculum, AVPRs in the dentate gyrus and CA3 region (Zaninetti and Raggenbass, 2000). Initial studies in rodents seemed to indicate that AVP could increase memory, antagonize amnesia, and facilitate memory consolidation (de Wied et al., 1993). A cellular basis for these effects arose with the discovery that inhibitory neurons in the CA1 area could be directly excited by AVP and OT, whereas pyramidal neurons were inhibited (Mühlethaler et al., 1982, 1984; Tiberiis et al., 1983). OT and its structural analogs were more potent than AVP, suggesting an activation of OTRs (Mühlethaler et al., 1984). In-depth analysis by Zaninetti and Raggenbass (2000) indeed confirmed that the inhibition of pyramidal neurons was caused by an excitatory action of OT on GABAergic interneurons that were mostly located within the stratum pyramidale (Figure 5B). The excitatory effects of OT were restricted to the soma and/or dendrites of these interneurons, and, although OTRs have been found in hippocampal synaptosomal membranes (Audigier and Barberis, 1985), no evidence was found for direct excitatory effects on the axon terminals. This hippocampal action of OT appeared species dependent. For example, in the guinea pig, the hippocampus shows no OT binding sites and CA1 hippocampal interneurons are unaffected by OT (Raggenbass et al., 1989).

Whereas this neuromodulation by OT was acute and reversible within minutes, AVP effects in the hippocampus have in many cases been shown to last much longer. Typically, they occur at concentrations of only a few pM (compared to 100 nM for acute effects) and cause, without directly affecting neuronal excitability, a potentiation of synaptic transmission that emerges over several minutes and outlasts the AVP application for up to an hour. These effects can also be produced by shorter AVP fragments (e.g., AVP4-8), but they are insensitive to V1a receptor blockade (Du et al., 1998). Thus, it remains unclear which or whether specific receptors are activated and which intracellular pathways are involved. Similarly, long-term

OT applications (3 hr) can induce LTP at the Schaffer-CA1 synapse. These effects depended on CREB-phosphorylation through a MAP kinase pathway and were also not mediated through an acute neuromodulatory mechanism (Tomizawa et al., 2003). It is possible that neuropeptides play a trophic role in the hippocampus, as also proposed in the spinal cord (see below). For example, repeated OT injections in the dentate gyrus can increase neurogenesis (Leuner et al., 2012). Similarly, Iwasaki et al. (1991) noted a neurotrophic action of AVP, but not OT, in explanted spinal cord cultures. Tribollet et al. (1991; 1994) demonstrated a transient increase of AVP binding in motoneurons in neonatal spinal cord and similarly 14 days after axotomy, both suggestive of a trophic activity.

The above findings seemed promising for treating patients affected by memory problems and have indeed been followed by clinical studies. Whereas some studies showed an improvement in memory mediated by AVP, others reported mixed findings or were unable to show positive results (reviewed in Viviani and Stoop, 2008). Though OT-containing axons originating from the PVN are present in the hippocampus (Buijs, 1978; Knobloch et al., 2012), the precise function of hippocampal OT signaling remains as of yet unknown. It is possible that OT may affect network oscillations or synchronization or affect synaptic plasticity (Freund and Buzsáki, 1996). Interestingly, following generalized seizures, a selective activation of OT-expressing neurons (and a long-lasting upregulation of OT mRNA) occurs in the PVN (Sun et al., 1996). This raises the intriguing possibility that OT, by enhancing inhibitory transmission in the hippocampus, may act as an endogenous anticonvulsant (Zaninetti and Raggenbass, 2000).

Lateral Septum

The septum and hippocampus are heavily interconnected, suggesting these two structures share similar functions. The hippocampus sends a massive, glutamatergic innervation to the lateral septum (LS), with progressively more ventral parts of the hippocampus innervating progressively larger and more ventral LS regions (Risold and Swanson, 1997). Thus, the ventral hippocampus innervates a much greater volume of the LS than does the dorsal hippocampus. The caudal part of the LS receives projections from the CA3, whereas the CA1 hippocampus and subiculum project to the rostral LS (Trent and Menard, 2010). The ventral LS is rich V1a receptors (Freund-Mercier et al., 1988), as well as OTRs, which can also be found in the dorsal LS (Curley et al., 2012). The LS is densely innervated by AVPergic axons, originating mostly from AVPergic neurons in the BST and the amygdala (Caffé et al., 1987) and by OTergic axons originating from neurons in the PVN and SON (Knobloch et al., 2012). A number of studies have indicated that AVP and OT signaling in the LS is important for social recognition and related social behaviors including maternal care (Bielsky and Young, 2004; Bielsky et al., 2005; Caffé et al., 1987; Veenema et al., 2010, Curley et al., 2012). In rats, septal administration of AVP increases short-term social recognition memory (Dantzer et al., 1988) and rescues social memory of Brattleboro rats that naturally lack AVP (Engelmann and Landgraf, 1994). Similarly, in mice, overexpression of V1a receptors in the LS increases social recognition memory (Bielsky et al., 2005), and viral re-expression of V1a receptors in the LS in V1aR KO mice can completely rescue deficits in short-term social recognition (Bielsky et al., 2005). Furthermore, levels of OTR expression in the LS have been correlated with frequency of nursing by lactating females (Curley et al., 2012) These studies suggest the LS may play an important role for the social and affective bonds that AVP and OT modulation has been found to affect in humans (Kosfeld et al., 2005; Storm and Tecott, 2005).

In spite of these important behavioral implications, studies on the neuromodulatory actions of AVP and OT in the septum at the cellular level are relatively sparse. AVP applied by iontophoresis (Joëls and Urban, 1982) or by bath perfusion on in vitro slices (Raggenbass et al., 1987) showed an excitation in 30%–40% of septal neurons. Effects were concentration dependent and were mediated by a V1a-R that was also somewhat sensitive to OT (Raggenbass et al., 1987). Further experiments revealed a more complex picture, in which AVP can directly excite a subpopulation of GABAergic inhibitory neurons and, through these, indirectly inhibit a large population of inhibitory projection neurons (see Figure 5A). All effects were mediated by V1aR, without involvement of the V1bR (Allaman-Exertier et al., 2007). As a result AVP would lead to a disinhibition of target structures among which are the hypothalamic nuclei involved in behavioral tasks (Risold and Swanson, 1997) important for social recognition. The direct excitatory effects of AVP on GABAergic neurons may possibly also modulate the theta rhythm that is known to originate in the septal area and propagate to the hippocampus (Urban, 1998). No effects of OT in the dorsal LS seem to have been reported. In addition to these acute neuromodulatory effects, long-lasting facilitating effects of AVP on evoked postsynaptic potentials that persist well beyond the period of AVP administration have been reported. As in the hippocampus, these effects of AVP appeared at low concentrations (1 pM). This long-lasting effect could *not* be blocked by a V1 receptor antagonist (Van den Hooff and Urban, 1990).

Taken together, these findings indicate that in the hippocampus and LS, AVP and OT can exert reversible neuromodulatory effects as well as long-lasting potentiating effects on synaptic transmission. It is possible that neuromodulation of oscillatory rhythms may in addition affect synaptic plasticity and memory processing, such as required for social memory and cognition. In view of the adjacent expressions of V1aR and OTR in both these reciprocally connected regions, it remains to be explored to what extent OT and AVP can complement each other's functions.

Opposite Effects on Sensory and Motor Regulation

Spinal Cord

Both OT and V1aRs have been found in the spinal cord, with a striking segregation of OTRs in the dorsal and AVPRs in the ventral part (Figure 5E). This is matched by OT projections from the hypothalamus terminating in lamina I-II (Breton et al., 2008) and AVP projections to the ventral parts (Hallbeck and Blomqvist, 1999). The specific OT-agonist [Thr4Gly7] OT (TGOT) activates here a subpopulation of lamina II glutamatergic interneurons that project onto GABAergic interneurons. OT thereby elevates inhibition of the nociceptive afferent messages that originate from C and Aδ primary afferents. These findings could explain the analgesic effects that have been reported for

OT in both humans and rodents (Schorscher-Petcu et al., 2010). Expression of V1aRs is particularly high in the spinal cord of young rats, declining in older individuals (Liu et al., 2003). AVP excites motoneurons via a postsynaptic mechanism involving suppression of a resting K^+ conductance and activation of a cationic conductance in laminae VIII and IX of the lumbar spinal cord and in the sexually dimorphic pudendal motoneurons in segments L5 and L6, which play a critical role in sexual and eliminative functions (Ogier et al., 2006). AVP can also excite glycinergic interneurons that innervate these motoneurons, thereby indirectly increasing inhibition (Kolaj and Renaud, 1998; Oz et al., 2001). However, this effect was also observed with the specific OT agonist TGOT, and it is therefore possible that this was instead mediated by OTRs in layers I and II and excitation of inhibitory interneurons that also send collaterals to these motoneurons (Liu et al., 2003; see Figure 5B). This circuit could thus orchestrate the opposite, inhibition by OT of sensory input and motor output with the excitation by AVP of motor output, in a way resembling their opposite effects in the CeA.

Facial Motor Nucleus VII and Hypoglossal Nucleus XII

In the neonatal rat, AVP binding sites are highly expressed in the facial motor nucleus (VII, Figure 5C). Application of AVP generates a sodium current that is voltage gated, noninactivating, and TTX resistant. It is possible that AVP exerts this neuronal action by directly activating a receptor-coupled adenylate cyclase or, alternatively, by activating a PKC through the PLC pathways that suppresses the activity of a guanine-nucleotide binding protein which in turn inhibits the AC complex (Raggenbass et al., 1991). An intricate interaction between AVP and OT on local circuits seems to occur in the hypoglossal nucleus, situated in the myelencephalic part of the brainstem at the same caudal-rostral level as the dorsal vagal complex and nucleus ambiguus, though more medially (Figure 5D). Hypoglossal (XII) motoneurons innervate both extrinsic and intrinsic muscles of the tongue and play an essential role in suckling, swallowing, breathing, chewing, and vocalization (Wrobel et al., 2010). XII motoneurons from young rats express V1a receptors and are strongly activated by AVP. Besides these direct excitatory effects, both AVP (through V1a) and OT can also enhance glycinergic and GABAergic transmission from local interneurons onto the XII motoneurons (Raggenbass, 2008, Reymond-Marron et al., 2005; Wrobel et al., 2010). Glycinergic and GABAergic input in very young animals can be excitatory and this has been proposed to play a role in the development of motor neuronal circuits (Singer et al., 1998). In both invertebrates and vertebrates, complex networks of motoneurons and interneurons can constitute the neuronal substrate underlying rhythmic motor patterns like breathing, chewing, walking, or swimming. It is possible that the combined actions of AVP and OT on this circuitry play an important neuromodulatory role or possibly even underlie this rhythmicity.

Effects on Central Pattern Generators

In vertebrates, central pattern generators (CPGs) in the spinal cord are involved in the control of locomotion (Goulding, 2009) and can be activated and regulated by a variety of neuromodulators (Marder and Bucher, 2001). The proliferation of V1aRs and OTRs suggests that AVP and OT, by acting on motoneurons as well as on interneurons or premotor neurons, may function as such neuromodulators. Indeed, Pearson et al. (2003) demonstrated that AVP or OT can activate networks of neurons in isolated neonatal mouse spinal cord to generate locomotor-like activity. Interestingly, a recent study by Wagenaar et al. (2010) suggests that such a role of AVP and OT can be traced back far in evolution. Thus, in medicinal leeches (Hirudo), AVP/OT homologs [Arg^8]conopressin, hirudotocin, and annetocin could exert powerful effects on a CPG located in midbody ganglia M5 and M6, the ganglia that control the male and female genital structures. As a result, these compounds elicit twisting behaviors and a further complete sequence of behaviors in preparation of copulation that are normally only induced by exposure to a specific female pheromone. It thus appears that the effects of members of the AVP/OT family in the spinal cord may be associated with a reproductive function of these hormones throughout the animal kingdom (Wagenaar et al., 2010).

In this context, the OTergic and AVPergic projections from the hypothalamus, so well preserved over evolution, may play an important role. The paraventricular nucleus plays a decisive role in maintaining homeostasis by regulating autonomic functions such as stress response; cardiovascular, breathing, and renal control; and food intake and body weight regulation. A direct communication between the paraventricular nucleus and somatic motor centers could allow rapid integration of autonomic response with motor behavior. For example, an increase in drive for food intake could correlate with an AVP-mediated increase in the excitability of motoneurons controlling tongue and facial muscles, i.e., XII and VII motoneurons. The fact that V1a receptors are preferentially expressed in motoneurons of newborn and young animals (Tribollet et al., 1991; Liu et al., 2003) suggests that this hypothalamic-motor interaction may be critical early in development in shaping neuronal networks involved in motor control (Reymond-Marron et al., 2006). Similarly, reproductive behavior requires specific coordinated motor behavior, such as those underlying lordosis in female rats. Neuromodulatory roles of OT and AVP may therefore extend throughout many circuits underlying this behavior, starting from the sensory triggers to the motor output.

Toward an Integrated View of OT and AVP Effects on Neural Function

In the above section, a number of neuromodulatory effects by AVP and OT have been summarized, with their effects on different nuclei considered as part of a common denominator in the context of different behavioral systems. In the olfactory system, OT and AVP seem to exert their effects in concert on subsequent stations of the pathway, underlining their importance in the context of social cognition and mating behavior. In view of their sensitivity to estrogen and progesterone, it seems important to separate their effects according to gender and period. In the central amygdala, key structure for raising alert, and in the sympathetic and parasympathetic system with which the CeA is connected, OT and AVP exert strikingly opposite effects. A similar separation into opposite effects seems to operate in memory and learning and in the spinal cord at the dorsal sensory input versus the ventral motor output.

For the moment, it remains unclear how the endogenous supply systems of OT and AVP are handling and coordinating

these modulations. Is there a massive nondistinctive release on various targets once the OT/VP production and release machinery has been activated, or is it possible that a more refined activation at the cellular production level takes place? Can we distinguish different neuronal populations within the OT or AVP producing neurons in relation to the behavioral systems that they innervate? If so, do neuronal populations that produce OT and AVP coordinate their activities according to the brain regions and systems that they innervate (and oppositely regulate)? With the rapid discovery of the precise promoters and enhancing elements (Gainer, 2012) that regulate their specific expression, it is becoming possible to specifically target expression of various protein tools in (part of) these cellular factories, to dissect in detail these possibly very refined and specifically targeted regulatory pathways. This may make it possible, in the future, with a combination of electro-optical stimulation and pharmacological application, to target more precisely only parts of the endogenous regulation. The results of a further detailed understanding of the regulatory mechanisms may lead to the identification of novel targets for pharmaceutical developments counteracting a large variety of symptoms linked to anxiety, memory formation, heart beat, and sexual behavior.

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